November 11, 1946

Dr. J. Lederberg
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Dear Josh:

Received your letter of November 6th and read it with great surprise. The one point which you say is not clear to you is the one that I thought I had explained most thoroughly, both in my lecture as well as in the paper. You ask the following questions:

1. Why should the presence of exogenous nitrogen affect this process if the substrates are simply competing on unstable enzyme molecules? 2. Why are the enzymes less unstable in the presence of azide?

It seems to me that just removing the question mark should lead one to the solution. There are two possible reasons why an enzyme might disappear. One is that it is inherently unstable, and the other is that it is maintained by continual synthesis at a rate equal to its breakdown, and that the synthetic mechanisms for all the various enzymes compete with one another for both energy and protein. The fact that this exogenous nitrogen can abolish interaction effects would seem to indicate that nitrogen supply is a critical factor in this competitive interaction. The effect of azide fits in very well with this idea. Azide can prevent a cell from forming enzymes as well as assimilate nitrogen, and all the evidence indicates that in the presence of azide the nitrogen turnover is completely abolished, which must mean that all competitive interactions between enzyme-forming systems must also disappear. Consequently, it is not surprising to find that azide can freeze the enzymatic constitution of the cell. In other words, these results indicate that the stability of an enzyme depends upon the competitive relation which its synthesizing mechanism has with the other protein-synthesizing systems in the cytoplasm. If a particular enzyme is formed by a synthetic mechanism which is a relatively poor competitor, then it will disappear rapidly as soon as protein turnover is permitted if it is not stabilized by substrate. In the absence of substrate, the

only way to keep such an enzyme in existence is to prevent any demand for protein, in other words, stop all new protein or enzyme formation.

You mention "a second competing substrate". The substrates do not compete directly with one another in any way, according to our present concept. If you take a cell adapted to one substrate and remove it and then put another substrate in, the first enzyme system will disappear as the cell becomes adapted to the second substrate, but the competition which is evident in this phenomenon by the disappearance of the first enzymes as the second makes its appearance is not at the substrate level but must be below the enzyme-precursor level, that is, at the level of competition for protein.

I saw your note in Nature and it looks very good. I notice from your letter that you are talking about "crossing". Is this a verbal or scientific advance?

Your projected experiments with lactose fermentors is a good one but I should like to introduce a note of pessimism. Hershey and I tried this some time ago and did not get very good results. However, we did not use irradiated, induced mutations, and so perhaps you will have better luck. Besides, we did not have the advantage of your more precise methods, and particularly, the great advantage that you have of being able to tag that in some other way so as to follow them more carefully.

Just so you will not complain that I am completely uncommunicative about our own results, I may note that we are having some difficulty in identifying the nature of adaptin. The difficulty is magnified by the fact that the damned compound is extremely unstable. So far there is a complete parallelism in its properties with the penumococcus transforming agent. We will soon have some enzymatic analysis on it since we have just obtained some highly purified desoxy-ribose nuclease. Some other experiments along other lines have come out in a very interesting fashion. I will tell you about them some other time.

Good luck and give my regards to Ed and Dave, and keep me informed as to your results.

Sincerely,

S. Spiegelman

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